REMARKS

This amendment is submitted after final rejection under 37 CFR 1.116 because Applicants believe that all claims now presented are in condition for allowance. In any event entry of this amendment will place the application in better form for appeal. No new matter has been added and no new issues have been raised. Finally Applicants are submitting this amendment in response to points first raised by the Examiner in the last office action and so Applicants could not have filed their response at an earlier date.

Applicants have canceled claims 6 through 11, and added new claims 12 through 30. Antecedent basis for the new claims covering synergistic antispasmodic and analgesic compositions may found in the specification as follows:

Claims 12 and 13, and dependent claims 14 through 17: Antecedent basis may be found in Table 3 on page 6 of the specification.

Claim 18 and dependent claims 19 through 21: Antecedent basis may be found in Part (D), page 11, line 22 to page 12, line 5, especially page 11, line 28 with the antecedent basis for the 150 parts tolperisone and 30 parts dextromethorphan.

Claims 22 through 26: Antecedent basis may be found on page 5, line 19 through page 6, line 10, including Table 2 on page

6 of the specification and the weight ratios of tolperisone and dextromethorphan stated on page 6, line 6.

Claims 27 through 30: Antecedent basis may be found on pages 7, 8 and 9 of the specification, especially in Tables 4 and 5.

Thus claims 12 through 30 are now in this application and are presented for examination.

The Examiner has agreed that Applicants' amendments to the claims and arguments submitted in their last response of 25 April 2008 overcame the Examiner's rejection of the claims for improperly claiming the invention and the Examiner's rejection of the claims as obvious in view of the prior art cited in the first official action. However, the Examiner conducted a second search of the prior art as well as re-read the background portion of the present application, and has decided to give the Applicants a new rejection of all claims as obvious in view of the prior art. The rejection is FINAL.

The principal reference that the Examiner is now relying upon to support the obviousness rejection is US Patent 5,840,731 to MAYER et al. In addition the Examiner is relying upon the WEINBROUM et al reference cited in the present application on page 2, first full paragraph, and BOSE, Methods Find Exp Clin Pharmacol. 1999 Apr; 21(3): 209 to 213, in combination with MAYER. The Examiner is citing BOSE to establish that tolperisone and eperisone

are analgesic compounds notwithstanding the statement on page 1 of the application that there is no unambiguous clinical evidence for the analgesic effect of tolperisone. The Examiner is citing WEINBROUM et al for its disclosure that dextromethorphan is both a per se analgesic and a known synergist for analgesics (pain control). The Examiner is citing MAYER et al for its disclosure that pharmaceutical compositions containing both an analgesic and a muscle relaxant may be enhanced using an NMDA, in particular, dextromethorphan to enhance the therapeutic effects of these compounds.

The Examiner argues essentially that MAYER et al discloses pharmaceutical compositions for treating pain that contain an analgesic, an NMDA antagonist such as dextromethorphan, and a muscle relaxant. The reference indicates in col. 2, line 49 that the pharmaceutical compositions may be used to treat either acute pain or chronic pain. The Examiner also points out that the NMDA, especially dextromethorphan, enhances the efficacy of the composition, by either reducing the amount of the analgesic required or by increasing the level of pain relief provided by the same amount of the analgesic. The Examiner points out that in col. 5 of the reference, a wide variety of routes of administration of the pharmaceutical composition are disclosed.

The Examiner admits that the specific muscle relaxants disclosed and claimed in the present invention are not disclosed in MAYER et al. The MAYER et al reference discloses in col. 4, lines

30 to 32, the following muscle relaxants: baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol, and orphrenadine. The Examiner argues, however, that there is nothing inventive about Applicants' substituting tolperisone or eperisone for one of the six specified muscle relaxants disclosed in MAYER et al since the prior art discloses that tolperisone or eperisone are known muscle relaxants.

The Examiner further argues that it would have been obvious to use the presently claimed compositions and methods of treatment administering these compositions to either treat spasticity since both tolperisone and eperisone are known to effectively treat spasms or as an analgesic because the BOSE reference discloses that eperisone may be used to treat pain associated with spondylosis, which appears to be a form of arthritis. The Examiner then relies on the WEINBROUM et al reference for its disclosure that dextromethorphan is known to treat pain, and so the Examiner finds nothing surprising or unobvious that the claimed compositions or methods of treatment are effective in treating either pain or spasticity.

Lastly the Examiner argues that method of treatment claims 16 and 17 are directed to an obvious treatment since Applicants agree that tolperisone and eperisone are both known for the treatment of spasticity and the pain associated therewith. MAYER et al discloses that dextromethorphan enhances the effects of analgesics.

There are some significant differences between the pharmaceutical compositions disclosed in MAYER et al and the pharmaceutical compositions according to the present invention. The Examiner admits that MAYER et al does not disclose tolperisone or eperisone as the muscle relaxant. Applicants strongly disagree that either tolperisone or eperisone is the equivalent of the baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol, and orphrenadine disclosed in the reference as a muscle relaxant. Structurally tolperisone and eperisone both have a p-alkyl-benzoyl functional group at one end of the molecule and an N-piperidinyl functional group at the other end of the molecule with a branched propylene chain in the middle. None of the six muscle relaxants disclosed in the MAYER reference has a structure even remotely similar. Furthermore according to page 1, third paragraph of the present application, the modes of action of centrally acting muscle relaxants can be different. In view of both the difference in structure and the difference in mode of action of providing muscle relaxant activity, substituting tolperisone or eperisone, the latter compound disclosed in BOSE, for the six specified muscle relaxants in MAYER would not be merely routine because the compounds have vastly different structures, vastly different mechanisms of anti-spasmodic activity, and so are not art-recognized equivalents.

Another significant difference between the presently claimed pharmaceutical compositions and those of MAYER et al are the kinds of pharmaceutically active ingredients in each respective composition. Applicants' claimed compositions are limited in terms of the active ingredients to two active ingredients: tolperisone or eperisone as the analgesic compound or the compound for treating spasticity and dextromethorphan as the compound that either potentiates tolperisone or eperisone as the analgesic compound or that combined with either tolperisone or eperisone is synergistically effective for treating spasticity. The MAYER et al compositions require compositions with three active ingredients including (1) either an opioid type analgesic such as codeine or a nonopioid type analgesic such as acetaminophen or aspirin. Neither of these compounds is a part of the Applicants' presently claimed compositions nor can these compounds even be included in Applicants' claims as active ingredients since Applicants' composition claims use the limiting words - which consists essentially of -. See claim 12, line 2. MAYER et al further requires (2) a sedative, skeletal muscle relaxant, as explained hereinabove, completely different from tolperisone or eperisone and (3) a non-toxic N-methyl-D-aspartate receptor antagonist, which may be dextromethorphan. Thus the MAYER et al compositions are different from Applicants' compositions for two reasons: MAYER et al discloses muscle relaxants different from tolperisone or eperisone and MAYER et al

requires additional art-established analgesic agents, designated as opioid or non-opioid analgesic agents, that are excluded from the presently claimed compositions. Of course neither tolperisone nor eperisone is either an opioid analgesic agent or the kind of non-opioid analgesic agent defined in MAYER et al in col. 1, lines 5 to 13.

According to the second paragraph of page 1 of the present application and according to the BOSE reference relied upon by the Examiner, tolperisone and eperisone, respectively, are disclosed as compounds that treat the pain of spasticity. The Examiner will not accept that a compound that treats spasticity is not necessarily an analgesic too since spasms are painful. Applicants point out that muscle relaxant drugs are only useful in relieving pain associated with spasticity, but are not necessarily effective in the treatment in the treatment of most pain syndromes (e.g. neuropathic pain). The use of tolperisone and eperisone is restricted to disease areas where pain is caused by abnormally increased muscle tone. Furthermore the data in BOSE directed to the analgesic effect of eperisone refer to a situation where the disease of vertebrae (cervical spondylosis) causes painful muscle spasms, which is responsive to muscle relaxants. The data presented according to the present application prove that tolperisone, in combination with dextromethorphan, has an anti-allodynic effect in a neuropathic pain model, where muscle spasms do not play a role in the

development of th pain state. This anti-allodynic effect indicates, rather than a limited anti-spasmodic effect for treating the pain of spasms, a full spectrum of analgesic activity that is neither disclosed nor suggested in the cite prior art references.

There is also the question as to whether dextromethorphan is per se an analgesic. Applicants state throughout the application that dextromethorphan is not an analgesic. See the first and second full paragraphs of page 2 of the present application. At the bottom of col. 1, MAYER et al also states that dextromethorphan is not per se an analgesic. Nonetheless according to WEINBROUM et al, cited by Applicants on page 2 of the application, first full paragraph, and relied upon by the Examiner in the present official action, dextromethorphan in some cases may be used, either per se or in combination with established analgesics, to treat acute pain. See Table 1 on pp 590 and 591 of WEINBROUM. According to the WEINBROUM et al abstract and according to the conclusions expressed on page 591, last paragraph, dextromethorphan is ineffective in the treatment of chronic pain but on page 594 under - Conclusion -, dextromethorphan is indicated as effective in combination with "conjointly administered analgesics" for treating acute pain. The Examiner concludes from this reference that the dextromethorphan is either an analgesic used per se, an analgesic

used in combination with other analgesics or a compound that enhances the effects of analgesics.

Even if there may be room for the Examiner and the Applicants to have a difference of opinion as to whether tolperisone and eperisone are known per se for the treatment of pain and whether dextromethorphan is known to be effective in the treatment of acute pain, either per se or in combination with an established analgesic, Applicants emphasize, however, regarding all claims now presented that the Examiner has overlooked the synergistic aspects of the combination of tolperisone or its homolog eperisone with dextromethorphan in the treatment of spasticity. Even if tolperisone or eperisone is known per se to treat spasticity and even if dextromethorphan were known to potentiate the effects of analgesic compositions that also contain muscle relaxants from MAYER et al, the Applicants' data in the specification in Tables 2 through 6 establish that the Applicants' combination of tolperisone or eperisone with dextromethorphan is synergistically effective in treating spasticity, and that such a composition is patentable unless the synergism between these particular compounds would have been expected from reading the prior art.

The Examiner has not found a reference that would suggest that the combination of tolperisone or eperisone with dextromethorphan would have been synergistically effective in treating spasticity. The data in Table 3 on page 6 of the

specification show that dextromethorphan has almost no per se antispasmodic activity and that tolperisone per se has some anti-spasmodic activity, but the anti-spasmodic effect of the combination of tolperisone and dextromethorphan in treating spasticity is more than the additive effect of dextromethorphan and tolperisone; it is synergistic. See page 10, line 9 to page 11 at the end of Applicants' last response. The MAYER et al reference discloses compositions that contain one or more established analgesics, an anti-spasmodic agent and dextromethorphan. Neither the analgesics nor the anti-spasmodic agents are either tolperisone or eperisone. Furthermore the dextromethorphan is disclosed as potentiating the analgesic compound in the composition, not the anti-spasmodic compound (see col. 2, lines 30 to 36 of MAYER) and so there is nothing in MAYER that would indicate that the synergism between tolperisone or dextromethorphan and dextromethorphan as covered in present claims 12 through 17 in treating spasticity would have been expected from reading the prior art. There is no mention in col. 4, following line 32 of MAYER et al that dextromethorphan potentiates the anti-spasmodic effects of these agents. And once again none of these anti-spasmodic agents is tolperisone or eperisone. Nor do Applicants find anything in either BOSE or WEINBROUM et al that would indicate that synergism would have been expected between these compounds in the treatment of

spasticity. Thus Applicants still believe that claims 12 through 17 as well as newly presented claims 18 are patentable.

Both MAYER et al and WEINBROUM et al indicate that dextromethorphan can potentiate analgesic compounds and WEINBROUM et al even indicates that dextromethorphan may have some per se effect against acute pain. There is nothing disclosed in either reference, however, that indicates that either tolperisone or eperisone would be useful in the treatment of pain, as opposed to being an anti-spasmodic, let alone that dextromethorphan would either potentiate the analgesic or anti-spasmodic effects of tolperisone or eperisone or would together with tolperisone or eperisone provide a synergistic analgesic effect, as opposed to the typical and structurally far removed analgesics disclosed in the references such as morphine, codeine, acetaminophen.

Applicants emphasize that they have presented data in the specification, especially in Table 3, that establish that the presently claimed compositions of claims 12 through 21 are surprisingly synergistically effective in the treatment of spasticity and chronic pain. These data meet the strict additivity test for synergism set forth in In re Kollman and Irwin, 201 USPQ 193 (CCPA 1979), a leading precedent on the requirements for proving a synergistic effect. Applicants have shown that the effect of these compositions at the stated weight ratios of the active ingredients is supra-additive and so at the outset these claims should be allowable over the cited prior art,

since Applicants have demonstrated synergism and the Examiner has not established that synergism would have been expected.

Applicants have additional data to establish that the presently claimed invention is directed to synergistic compositions and methods of treatment for treating spasticity and chronic pain to the data already presented in Table 4 on page 8 of the specification. Applicants are including these data in a Declaration Under 37 CFR 1.132, signed by two of the Applicants: Dr. Pal Kocsis and Dr. Istvan Tarnawa. The data in Figure 1 of the Declaration Under 37 CFR 1.132 together with the data in Table 4 from the specification are believed to be especially supportive of the patentability of claims 27 through 30 as directed to synergistic compositions and methods of treatment of spasticity and chronic pain.

Applicants now refer to claims 22 through 26. The data in Table 2 on page 6 of the specification relating to synergistic activity against tremor inhibition for dextromethorphan and tolperisone together with the statement in the last paragraph on page 5 of the specification that dextromethorphan exerted per se almost no tremor inhibition meet the additivity test for establishing synergistic anti-spasmodic activity. One again Applicants have demonstrated synergism and the Examiner has not demonstrated that synergism would have been expected.

In view of the above Applicants have submitted sufficient data in the specification and in the Declaration under 37 CFR 1.132 in Figure 1 to establish that all of the claims now presented are directed to synergistic compositions for treating spasticity and chronic pain, and the Examiner has not provided evidence that such synergism would have been expected.

Now Applicants turn to Figure 2 in the Declaration Under 37 CFR 1.132. The data in Figure 2 relate to the inhibition of spinal reflexes in the rat hemiselected spinal cord preparation, which is a suitable method for evaluating drug effects on spinal neuronal functions having important roles in in the effects of (e.g. muscle relaxants or analgesic agents). Applicants have performed an in vitro study to compare the spinal action of tolperisone alone and in the presence of dextromethorphan. Applicants measured the reflex inhibitory action of tolperisone itself and in combination with dextromethorphan. The results and the statistic analysis are shown in Figure 2 and in the caption following the figure. The results are presented as an isobologram.

The IC_{50} values for both tolperisone per se and dextromethorphan per se were determined for inhibiting the ventral root reflex (MSR). The IC_{50} values for inhibiting MSR for dextromethorphan were plotted on the X-axis and the IC_{50} values for inhibiting MSR for tolperisone were plotted on the Y-axis. The straight line connecting the two plotted IC_{50} values

represents the additive effect of the tolperisone and dextromethorphan IC_{50} values for inhibiting MSR for each compound. The experimental IC_{50} values of the combination tolperisone and dextromethorphan is plotted as the closed square toward the lower left side of the isobologram. Since the actual experimental data for the combination of tolperisone and dextromethorphan IC_{50} values for inhibiting MSR lie well below the straight line, the effect is clearly supra additive or synergistic.

Applicants conclude that in view of the differences between the presently claimed invention and the disclosures in MAYER et al, BOSE and WEINBROUM et al, and in view of the synergistic activity against chronic pain and spasticity demonstrated by the combination of tolperisone and its homolog eperisone and dextromethorphan demonstrated in the application and in the Declaration Under 37 CFR 1.132, all claims now presented are patentably distinguishable over the cited combination of references and that the Examiner should not reject any claim now presented as obvious under 35 USC 103.

In addition the Declaration Under 37 CFR 1.132 includes statements on the part of the declarants, both of whom are experts in this field of physiology, stating on pages 6 and 7 of the declaration, that the anti-spasmodic agents disclosed in MAYER et al, are not the equivalent of tolperisone or eperisone, explaining that the anti-spasmodic agents disclosed in MAYER et al have a different mechanisms of action from tolperisone and

eperisone, and specifically indicating that unlike the compounds disclosed in MAYER et al, tolperisone and eperisone exert the anti-spasmodic effects by the blockade of neuronal sodium and calcium ion channels.

Report of Interview

Applicants wish to thank Examiners Simmons and Federoff for granting a telephone interview with the undersigned attorney on 3 December 2008. Examiner Simmons has taken over the examination of this application from Examiner Rogers. In advance of the interview the undersigned faxed to Examiner Simmons a copy of this amendment and the accompanying Declaration Under 37 CFR 1.132. Examiners Simmons and Federoff indicated that they were both in general agreement with the Applicants' proposed response, including the amendments to the claims and the declaration. The Examiners specifically indicated that they agreed that the claims in the present amendment were directed to synergistic compositions, limited to two active ingredients, for treating spasticity or for treating spasticity and chronic pain, at the specified weight ratios between tolperisone or eperisone as the anti-spasticity agent and dextromethorphan as the compound, which together with the tolperisone or eperisone, synergizes the anti-spasticity effect and analgesic effect of the tolperisone or eperisone, according to the additivity test set forth in In re Kollman and Irwin, 201 USPQ 193 (CCPA 1979). The Examiners agreed

that no such invention is disclosed in MAYER et al which requires compositions with three active ingredients: an opioid or non-opioid analgesic, a specific anti-spasticity compound totally unrelated to tolperisone or eperisone, and dextromethorphan. However, the Examiners wanted the undersigned to confirm that the MAYER et al reference did not disclose or suggest a synergistic analgesic effect between a muscle relaxant similar to tolperisone or eperisone and dextromethorphan.

The undersigned noted that Applicants have presented data in the specification to establish synergism under the additivity test, between dextromethorphan and tolperisone or eperisone, proving a synergistic anti-spasmodic effect and a synergistic effect against chronic pain. The undersigned emphasized that all of the compositions disclosed in MAYER et al are compositions with three active ingredients, which include an analgesic agent, namely an opioid or non-opioid analgesic as defined in col. 3, line 56 to col. 4, line 7, a muscle relaxant, and dextromethorphan. There is no mention, in MAYER et al, of synergism either between all three components or between the muscle relaxant and dextromethorphan. There is certainly no mention or suggestion in MAYER et al of synergism between compositions that consist essentially of only two active ingredients: tolperisone or eperisone on the one hand and dextromethorphan on the other hand. The undersigned also again emphasized the significant difference both in terms of structure

and in terms of the mechanism of action between the muscle relaxants disclosed in MAYER et al in col. 4, lines 30 to 32 (e.g. baclofen) and tolperisone or eperisone according to the invention.

The undersigned emphasized that even though MAYER et al discloses in col. 3, lines 6 to 9, enhancing analgesia in general, the reference makes no mention of synergism between dextromethorphan and the opiate or non-opiate analgesics disclosed therein. Furthermore there is no disclosure in MAYER et al of synergism between the muscle relaxants disclosed therein (unrelated to Applicants' tolperisone or eperisone both structurally and in terms of mechanism of action) and dextromethorphan to exert an anti-spasmodic activity or even a disclosure of enhancement of the anti-spasmodic activity of the muscle relaxants by dextromethorphan.

The Examiners suggested that Applicants file their proposed Amendment Under 36 CFR 1.116 for consideration by the Examiners. The Examiners indicated that because the claims as now presented are materially different from the claims last presented, the Examiners might not enter the amendment under 37 CFR 1.116 because the amendment may raise new issues requiring further search, and new arguments requiring further response.

Applicants believe that all claims now presented are allowable over the cited combination of references and a response to that effect is earnestly solicited. Applicants enclose a

Petition to Obtain a one month extension of the term for response and PTO Form 2038 to permit the Applicants to charge payment of the fee to obtain a one month extension of the term to the credit card of the undersigned attorneys.

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Enclosure: Declaration Under 37 CFR 1.132 and attached reference